Registration Decision RD2012-21

Bacteriophage of *Clavibacter michiganensis subsp. michiganensis*

(publié aussi en français)

20 June 2012

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

ISSN: 1925-0932 (print)
1925-0940 (online)

Catalogue number: H113-25/2012-21E (print version)
H113-25/2012-21E-PDF (PDF version)

© Her Majesty the Queen in Right of Canada, represented by the Minister of Health Canada, 2012

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.

Registration Decision for Bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis*

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of AgriPhage-CMM Technical and AgriPhage-CMM, containing bacteriophage to suppress bacterial stem canker on greenhouse tomatoes caused by *Clavibacter michiganensis* subsp. *michiganensis*.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

These products were first proposed for registration in the consultation document[1], Proposed Registration Decision PRD2012-04, *Bacteriophage of* Clavibacter michiganensis *(subsp.* michiganensis*)*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2012-04.

For more details on the information presented in this Registration Decision, please refer to the Proposed Registration Decision PRD2012-04, *Bacteriophage of* Clavibacter michiganensis *(subsp.* michiganensis*)* that contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

---

1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act*"...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis*?

Bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* is the active ingredient in AgriPhage-CMM, which is a mixture of lytic bacteriophage strains highly specific to the causal pathogen of bacterial stem canker in tomato.

Health Considerations

Can approved uses of bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* affect human health?

Bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* is unlikely to affect your health when AgriPhage-CMM is used according to the label directions.

People could be exposed to bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* when handling and applying AgriPhage-CMM. When assessing health risks, several key factors are considered:

- the microorganism's biological properties (for example, production of toxic byproducts);
- reports of any adverse incidents;
- its potential to cause disease or toxicity; and
- the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

By nature, bacteriophage are viruses that are only capable of infecting bacteria. Bacteriophage are not capable of infecting animals, plants, or fungi and are not capable of producing any toxins outside their hosts because they are not metabolically active. Bacteriophage rely on the bacterial host's metabolism for reproduction and survival. Bacteriophage themselves are not considered to be toxic. Also, since the host bacterium, *C. michiganensis* subsp. *michiganensis*, does not produce toxins nor is it otherwise considered to be harmful to humans, the infection of these bacteria by bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* will not alter the bacterial population in a way that could be harmful to humans. Although the relative exposure of people to bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* may increase from the use of AgriPhage-CMM, there have been no reports of adverse effects or incidents resulting from the direct exposure to naturally occurring bacteriophage.

Residues in water and food

Dietary risks from food and water are not of concern

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Bacteriophage, including bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis*, are common in nature and there have been no adverse effects attributed to dietary exposure to natural bacteriophage populations. Outside their host bacteria, bacteriophage are not toxic and are incapable of producing toxins. Furthermore, since the host bacterium, *C. michiganensis* subsp. *michiganensis*, does not produce toxins nor is it otherwise considered to be harmful to humans, the infection of these bacteria by bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* will not alter the bacterial population in a way that could be harmful to humans.

Therefore, while the use of AgriPhage-CMM on greenhouse tomatoes will lead to transient increases in the population of bacteriophage over the short term, which could lead to an increase in dietary consumption, dietary risks are expected to be negligible. As well, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Consequently, dietary risks are minimal to non-existent. The PMRA has determined that the establishment of an MRL is not required for bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis*.

Occupational risks from handling AgriPhage-CMM

Occupational risks are not of concern when AgriPhage-CMM is used according to label directions, which include protective measures

Growers handling AgriPhage-CMM can come into direct contact with bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* on the skin, in the eyes or by inhalation. For this reason, the product labels specify that growers exposed to this product must wear waterproof gloves, long-sleeved shirts, eye goggles, a NIOSH-approved respirator (with any N-95, P-95, R-95 or HE filter for biological products), long pants and shoes plus socks.

For the bystander, exposure is expected to be much less than that of handlers and mixer/loaders and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What happens when bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* are introduced into the environment?

Environmental risks are not of concern

Following application, bacteriophage of *C. michiganensis* subsp. *michiganensis* is likely able to survive in the environment under favourable environmental conditions (i.e. low light, moist) but that over time populations of bacteriophage of *C. michiganensis* subsp. *michiganensis* are expected to return to natural background levels.

The effects of bacteriophage of *C. michiganensis* subsp. *michiganensis* on non-target organisms were considered. By nature, bacteriophage (phage) are only capable of infecting bacteria. Phage are not capable of infecting animals, plants, or fungi and are not capable of producing any toxins since they have no metabolism. Phage themselves are not considered to be toxic. Also, since *C. michiganensis* subsp. *michiganesis* does not produce toxins nor is it otherwise considered to be harmful to non-target organisms (other than tomato), the infection of these bacteria by bacteriophage of *C. michiganensis* subsp. *michiganensis* will not alter the bacterial population in a way that could be harmful to non-target organisms. Furthermore, minimal exposure to non-target organisms is anticipated from the use of AgriPhage-CMM to suppress *C. michiganensis* subsp. *michiganensis* in greenhouses.

Value Considerations

What is the value of AgriPhage-CMM?

Bacteriophage for *Clavibacter michiganensis* subsp. *michiganensis*, the active ingredient in AgriPhage-CMM, suppresses bacterial stem canker caused by *Clavibacter michiganensis* subsp. *michiganensis* in greenhouse tomato.

AgriPhage-CMM can be applied for seedling treatment and hydroponic greenhouse treatment.AgriPhage-CMM is a novel pesticide and has a completely new mode of action, and offers an additional tool for managing bacterial stem canker, a destructive bacterial disease on greenhouse tomato. There are currently very few registered products for this disease. AgriPhage-CMM may be used as a component of an IPM strategy for bacterial stem canker on greenhouse tomato.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the label of AgriPhage-CMM to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

As with all microbial pest control products, there are concerns with users developing allergic reactions through repeated high exposures to bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis*. Therefore, anyone handling AgriPhage-CMM must wear waterproof gloves, long-sleeved shirts, eye goggles, a NIOSH-approved respirator (with any N-95, P-95, R-95 or HE filter for biological products), long pants and shoes plus socks. All early-entry workers to treated sites will be required to wear personal protection equipment until the spray has dried, including a NIOSH-approved respirator until spray mists have settled.

Environment

As a general precaution, the label prohibits the direct application of the product to aquatic habitats (such as lakes, streams and ponds). The label also directs growers to not allow effluent or run-off from greenhouses containing this product to enter lakes, streams, ponds or other waters and to avoid contaminating surface water by disposal of equipment wash waters.

Other Information

The relevant test data on which the decision is based (as referenced in Proposed Registration Decision PRD2012-04, *Bacteriophage of* Clavibacter michiganensis *(subsp.* michiganensis*)*) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision, www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/publi-regist/index-eng.php#rrd) or contact the PMRA's Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act*.

Appendix I Comments and Responses

1. Comment on the mode of action of Bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis*

Comment:

The Overview of the PRD2012-04 under the heading 'What is Bacteriophage of *Clavibacter michiganensis* (subsp. *michiganensis*)' incorrectly states that the 'phage integrates its genome into the bacterial DNA'. Similarly, Section 1.4 incorrectly states that the 'bacteriophage may enter a period of inactivity after which their DNA is incorporated into the bacterial DNA, which is passed on to succeeding generations of bacteria'.

Response:

The PMRA acknowledges that the section entitled 'What is Bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis*' should read as follows:

> "Bacteriophage of *Clavibacter michiganensis* subsp. *michiganensis* is the active ingredient in AgriPhage-CMM, which is a mixture of lytic bacteriophage strains highly specific to the causal pathogen of bacterial stem canker in tomato."

Section 1.4 entitled 'Mode of Action' should read as follows:

> "The active ingredient in AgriPhage-CMM is a mixture of lytic bacteriophage strains for *Clavibacter michiganensis* subsp. *michiganensis*. Lytic bacteriophages are highly specific obligate intracellular parasites that affect host bacteria by penetrating host cells, multiplying in bacteria and killing the host cell at the end of the life cycle."